REMARKS

Reconsideration of the application is respectfully requested in view of the above amendments and following remarks. Claims 3, 4 and 49-66 were pending. Claims 3, 4 and 54-66 were withdrawn from consideration by the Examiner. Applicants have canceled Claims 3, 4 and 54-66. Currently, Claims 49 to 53 are pending in the present application.

Claims 3, 4 and 54-66 were withdrawn from consideration by the Examiner as being drawn to non-elected inventions. Claims 3, 4 and 54-66 have been canceled without prejudice to filing a divisional application directed to the subject matter claimed therein.

Applicants confirm election of the subject matter in Claims 49-53 as requested by the Examiner.

No new matter has been added to the above-captioned application by the above amendments. Applicants reserve the right to pursue the non-elected subject matter of the claims amended to comply with the restriction requirement in a divisional application.

REJECTION UNDER 35 U.S.C. 103(b) FOR OBVIOUSNESS

The Examiner rejected Claims 49-53 under 35 USC 103(a) as being unpatentable over Clark et al. (US Patent 5,597,797), and Hjorth et al., Society for Neuroscience Abstract Viewer and Itinerary Planner.

The Examiner indicated that Clark teaches the co-administration of various appetite suppressants, such as phentermine, which may be combined with a growth hormone and an insulin like growth factor-I (IGF-I), to treat or prevent obesity (See column 16, lines 26-65 and column 31, lines 55-57); and indicated that Clark teaches the combination treatment results by far in the greatest loss of fat, suggesting a synergistic effect on fat loss. The Examiner also stated that Clark teaches treatment of obesity-related disorders, such as polycystic ovarian disease or insulin resistance (see column 7, lines 56-67). The Examiner further stated that Hjorth teaches the administration of AM 251, 1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-N-1-

piperidinyl-1H-pyrazole-3-caroxamide, an inverse agonist at cannabinoid CB1 receptors, results in weight loss. The Examiner indicated that in view of the combined teachings of Clark and Hjorth, one skilled in the art would have been motivated to prepare and administer a composition comprising a combination of phentermine and AM 251 with a reasonable expectation of treating obesity. The Examiner stated that in the absence of evidence to the contrary, it is prima facie obvious to use in combination two or more compounds that have previously been used separately for the same purpose (See In re Kerkhoven, 205 USPQ 1069); and that it is not inventive to combine old ingredients of known properties, especially true in the field of obesity where combination therapies of known ingredients are conventional. The Examiner also stated that specific statements in the references that would spell out the claimed invention are not necessary to show obviousness since questions of obviousness involve not only what references expressly teach, but also what they would collectively suggest to one of ordinary skill in the art.

Applicants respectfully disagree. Applicants submit that Clark et al. (US 5,597,797) teaches that IGF-I has no significant effect on weight gain, although at 14 days weight gain occurred (10.0 ± 4.5 g) rather than weight loss (column 29, line 66 to column 30, line 1), and that based on data from Example II, food intake in the hGH infusion group was back to normal by day 14. Additionally, the Skottner reference, as cited in the Clark specification, states that food intake in young obese dwarf rats was unaffected by either GH or IGF-I infusions (Skottner et al., Endocrinology, 124: 2519-2526). Applicants submit that IGF-I is not an appetite suppressant as defined on page 40, lines 18-20 of the present invention, which requires a 5% reduction in total food intake or caloric intake or a selective reduction of intake of specific diet components. Additionally, the Clark reference states that IGF-I production is under the dominant stimulatory influence of GH (column 2, lines 29-31). As a result, it would not be obvious to combine two appetite suppressants (CB-1 antagonist/inverse agonist and phentermine) that work by different biological pathways to treat obesity based on the combination of GH and IGF-I disclosed in the Clark reference.

Applicants also submit that the Clark reference does not teach or suggest cannabinoid-1 receptor antagonists/inverse agonists in general, or AM251 specifically, as a monotherapy or as a combination therapy to treat or prevent obesity. Clark does not teach or suggest a composition comprising a cannabinoid-1 receptor antagonist/inverse agonist and phentermine to treat or prevent obesity. Additionally, there is no motivation in the Clark reference to use phentermine in a two component combination therapy, either with a growth hormone, or an insulin like

growth factor-I, or a cannabinoid-1 antagonist/inverse agonist, to treat or prevent obesity. Therefore, the composition of a cannabinoid-1 receptor antagonist/inverse agonist and phentermine is not prima facie obvious.

Applicants further submit that Hjorth reference teaches that AM-251 is a cannabinoid-1 receptor inverse agonist, and that AM-251 administration resulted in weight loss in cafeteria diet-induced obese (DIO) mice. The Hjorth reference does not teach or suggest cannabinoid-1 receptor antagonists/inverse agonists in general, or AM 251 specifically, as a combination therapy to treat or prevent obesity. The Hjorth reference does not teach or suggest a composition comprising a cannabinoid-1 receptor antagonist/inverse agonist in general, or AM251 specifically, and phentermine to treat or prevent obesity. Additionally, there is no motivation in the Hjorth reference to use AM251 in combination with phentermine to treat or prevent obesity. Therefore, the composition of a cannabinoid-1 receptor antagonist/inverse agonist, such as AM251, and phentermine is not prima facie obvious.

Applicants further submit that the combination of the Hjorth and Clark references does not teach or suggest cannabinoid-1 receptor antagonists/inverse agonists in general, or AM 251 specifically, as a combination therapy to treat or prevent obesity. There is no motivation in the Hjorth and Clark references to use AM251 in combination with phentermine to treat or prevent obesity or an obesity related disorder, including diabetes. Therefore, the composition of a cannabinoid-1 receptor antagonist/inverse agonist, such as AM251, and phentermine is not prima facie obvious.

As cited in the KSR opinion, "the combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results (See KSR International Co. v Teleflex Inc., 550 U.S. __ (2007) at 4; See also US v. Adams, 383 US 39, 50-52). Applicants submit that in the treatment of disorders associated with excessive food intake such as obesity, it is not predictable that adding a second anti-obesity agent that works via a different biological mechanism will result in additional or additive weight loss or food intake reduction. The following references show the unpredictability of combinations of anti-obesity agents. The Wadden reference states that the addition of orlistat to sibutramine did not induce further weight loss as compared with treatment by sibutramine alone (mean changes = +0.1 $\pm$ 4.1 kg vs + 0.5 $\pm$ 2.1 kg, respectively) (See Wadden et al., Obesity Research Vol. 8, No. 6, pp 431-437, Sept. 2000). The Wadden reference also states that the findings suggest that the

combination of sibutramine and orlistat is unlikely to have additive effects that will yield mean losses $\geq$ 15% of initial weight, as desired by many obese individuals. Further, the Erondu reference states that blockade of the NPY5 receptor with MK-557 (a neuropeptide Y 5 receptor antagonist) did not increase the weight loss efficacy of either orlistat or sibutramine (See Erondu et al. Poster, NAASO, Obesity Society Annual Meeting, Boston, MA, October 2006). The Wadden and Erondu references are enclosed. Applicants submit that based on these references, one of ordinary skill in the art would not be able to predict whether any particular combination of anti-obesity agents would lead to synergistic or even additive weight loss.

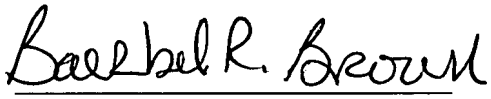
Applicants hereby submit the Declaration under 37 CFR § 1.132 of Dr. Alison Merwin Strack, which discusses *in vivo* studies of the AM251 and phentermine combination and their results. In the Declaration, Dr. Strack states that in her opinion, one of ordinary skill in the art would have found it surprising and unexpected that the combination of AM251 with phentermine dosing resulted in 1) supra-additive changes in the reduction of body weight; 2) supra-additive changes in the reduction of food intake; and 3) the amelioration of the hyperlocomotion observed with phentermine dosed alone.

Hyperlocomotion, or increased locomotor activity, is an undesirable side effect of phentermine administration in rodents (see Rowley et al., Synapse. 2000 Nov; 38 (2):167-76). Phentermine administration in humans is also known to cause the side effects of overstimulation, restlessness, elevation of blood pressure, cardiovascular palpitations, dizziness and insomnia (See Physician's Desk Reference, 61st Edition, page 1216, 2007). Therefore, it may be beneficial to decrease the increased locomotor activity and related effects in phentermine therapy.

Applicants respectfully submit that in view of the above arguments and study results, the composition comprising a cannabinoid-1 receptor antagonist/inverse agonist, such as AM251, and phentermine, is not obvious over the Hjorth and Clark references, and respectfully request reconsideration and withdrawal of the rejection of Claims 49-53 under 35 USC § 103(a).

Applicants believe that all of the rejections have been overcome and therefore earnestly solicit an early Notice of Allowance.

Respectfully submitted,

By 

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